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ORIGINAL ARTICLE

Can negative cardiac effect of proton pump inhibitor and high-dose H2-blocker have clinical influence on patients with stable angina?

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Summary
Background: Aspirin and anti-platelet drugs are used commonly for patients with coronary heart disease. Proton pump inhibitor (PPI) and high-dose H2-blocker were recommended for preventing NSAIDs-related ulcer. Previously H2-blocker reported to have some negative cardiovascular effects. Additionally, a recent *in vitro* study showed that PPI reduced cardiac contractility. In this study, we evaluated whether chronic administration of PPI and high-dose H2-blocker affects left ventricular function.
Method: Fifty-two stable angina patients were enrolled and classified into PPI group ([P]; lansoprazole: 15 mg/day, $n = 28$), H2-blocker group ([H]; famotidine: 40 mg/day, $n = 8$), and control ([C]; none or mucosal-defense drug, $n = 16$). Eligible patients showed normal cardiac function in initial catheterization without administrated PPI or H2-blocker. They received percutaneous coronary intervention and follow-up catheterization. We compared changes in ejection fraction (EF: %), end diastolic/systolic volume index (EDVI/ESVI: ml/m^2), and peak positive/negative dp/dt ($\pm$dp/dt: mmHg/s) in left ventricular angiography series.
Result: There were no significant differences among three groups regarding patient characteristics, backgrounds of angiographic and intervention, except for fewer

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smokers in [C]. Other drugs such as β- and Ca-blocker did not have effects on cardiac function except for aspirin during 255 ± 115 days follow-up. Rate of EF changes significantly decreased in [P], and tended to decrease in [H] (C: 3.8 ± 9.8%, H: −1.6 ± 7.6%, P: −2.1 ± 5.9%; $p < 0.05$ for [C] vs. [P]). Those of ESVI changes were significantly greater in [P], and tended to be greater in [H] (C: −4.5 ± 16.2%, H: 4.9 ± 15.5%, P: 7.3 ± 16.2%; $p < 0.05$ for [C] vs. [P]), though, EDVI changes' were similar (C: 2.5 ± 8.9%, H: 2.6 ± 3.6%, P: 1.6 ± 6.1%; p = ns). Rate of ±dp/dt—changes tended to decrease in [H] (+dp/dt: C: 3.9 ± 15.5%, H: −10.0 ± 25.2%, P: 0.3 ± 19.6%; p = ns, −dp/dt: C: −0.1 ± 19.5%, H: −8.5 ± 20.4%, P: 5.7 ± 27.7%; p = ns).
Conclusion: In this study, PPI and high-dose H2-blocker have EF-reducing tendency. However, these changes were small and these drugs seemed to exhibit little influence clinically.

Introduction

Aspirin and other anti-platelet drugs are essential to patients with ischemic heart disease [1,2]. The long-term use of these drugs can potentially lead to non-steroidal anti-inflammatory drugs (NSAIDs)-related peptic ulcer [3]. Proton pump inhibitor (PPI), high-dose H2-blocker, and prostaglandins are recommended for the prevention of such aspirin- or NSAIDs-related peptic ulcers [3], and these drugs are normally administrated to patients with ischemic heart disease including stable angina that have received percutaneous coronary intervention (PCI).

In a previous report, the use of high-dose H2-blocker was associated with several adverse effects such as bradycardia, sinus arrest, atrio-ventricular conduction disturbances, and cardiac decompensation [4]. However, another study reported that H2-blocker could modulate heart-rate variability, and has the possibility to inhibit the increase in the sinus rate and prevent ventricular ectopy [5].

Although PPI (omeprazole) administration did not lead to any changes in the cardiac performance of patients with congestive heart disease, as measured by impedance cardiography and mechanocardiography, after 1-week oral treatment with therapeutic doses compared with H2-blocker (famotidine) [6], PPI (pantoprazole) depresses cardiac contractility at higher concentrations *in vitro* by depressing Ca^{2+} signaling and myofilament activity [7].

It remains unclear in clinical practice, however, whether this negative effect on cardiac performance is attributable to long-term administrations of PPI and high-dose H2-blocker, and cardiac effects of these drugs assessed by invasive study have scarcely repoted. The purpose of this study was to investigate cardiac function in patients with stable angina using left ventricular (LV) angiography, and we compared pre-drug administration and post-PCI follow-up results.

Materials and methods

Patient selection

The present study was conducted according to the principles of the Declaration of Helsinki and approved by the local Ethics Committee. All study participants gave informed consent.

Patient selections are summarized in Fig. 1. Three hundred and fifty-five patients underwent elective PCI in our institute between June 2004 and March 2007. Patients were considered eligible for this study if: they had never undergone a cardiac catheterization study nor been administrated PPI or H2-blocker; had a history of stable angina or signs of myocardial ischemia in the presence of angiographically significant stenosis (>75%) in one or more coronary vessels; and had received PCI and undergone re-catheterization study involving LV angiography in a series of study.

Clinical exclusion criteria included: acute coronary syndrome, a history of unstable angina, myocardial infarction, and prior revascularization such as PCI or coronary artery bypass graft. Angiographic exclusion criteria included lesions requiring coronary artery bypass graft such as an unprotected left main trunk, lesions containing thrombi, and when left ventricular angiography revealed abnormal wall motions such as asynergy or diffuse hypokinesis. A total of 58 patients fulfilled the eligibility criteria: 32 patients with PPI (lansoprazole 15 mg: 28; omeorazole 20 mg: 3; rabeprazole 10 mg: 1), 10 patients with H2-blocker (famoidine 40 mg: 8; ranitidine 5 mg: 1; nizatidine 150 mg: 1) and 16 others (none: 13; other mucosal-defense drug: 3).

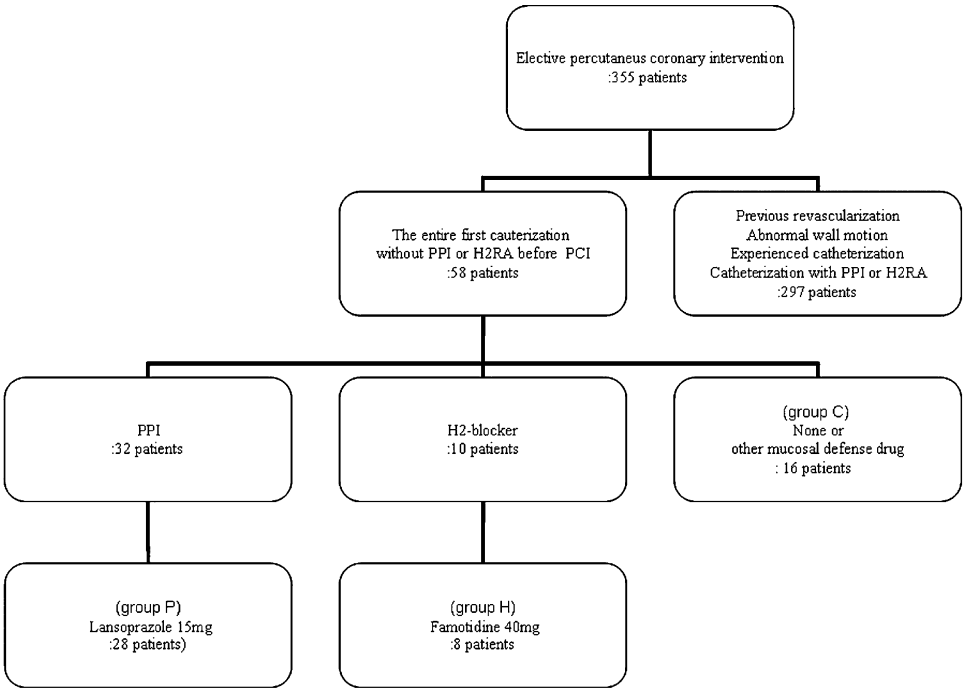

Figure 1 Flow chart of patient selection.

We classified patients into group P (lansoprazole 15 mg: $n = 28$), group H (famoidine 40 mg: $n = 8$), and control (group C: $n = 16$).

Procedures and antithrombotic treatment

All patients received oral therapy consisting of 100 mg of ticlopidine twice plus 81 mg of aspirin daily from 4 weeks before procedures, indefinitely. Cases in which ticlopidine was contraindicated received 100 mg of cilostazole twice. Following catheterization, all patients started to receive management with intensive pharmacotheraphy and lifestyle modification before PCI.

PCI was performed according to the standard protocol, based on angiographic and intravascular ultrasound findings. During intervention, patients received intravenous heparin (7000 U) followed by 1000 U of heparin every 60 min.

LV volume and pressure

LV angiography (30° right anterior oblique, 60° left anterior oblique) was performed just before coronary angiography. LV volumes were obtained by the biplane area—length method [8], via which end diastolic volume, end systolic volume, and ejection fraction (EF: %) were calculated. The end diastolic volume index (EDVI: ml/m^2) and end systolic volume index (ESVI: ml/m^2) were also calculated by dividing the end diastolic and end systolic volumes by the body surface area, respectively.

LV pressure was recorded in each patient with a pigtail catheter. The baseline was calibrated electronically by a transducer control unit before catheter insertion, and zero shift was adjusted to the level of the mid-chest position.

All cases showed a normal sinus rhythm, and five consecutive complexes were averaged to determinate ratio of change of ventricular pressure to change in time (peak positive dp/dt: $+dp/dt$: mmHg/s; peak negative dp/dt: $-dp/dt$: mmHg/s).

Statistical analysis

Categorical variables were compared using the χ^2 and Fisher's exact tests. Continuous variables were compared using t-tests. Categorical data are expressed as frequencies and percentages. p-Values < 0.05 were considered significant.

Repeated-measures ANOVA was used to analyze the effect on EF, EDVI, ESVI, $+dp/dt$, and magnitudious of $-dp/dt$. These were chosen as outcome variables, and predictor variables included Patient characteristics, angiographic and intervention backgrounds, and adjunct drugs.

Results

Characteristics of patients

Patient characteristics are summarized in Table 1. Among all patients, the mean age was 65 years; 64% were men; 73% had hypertension; 54% had hyperlipidemia; and 37% had diabetes. Although 27% of all patients were smokers, only 1 patient in the control group smoked.

Angiographic and intervention factors

Angiographic and intervention factors also are summarized in Table 1. Twenty-five patients (48.1%) had multi-vessel diseases, but only 7 patients (13.5%) requiring treatment for multi-vessels according to myocardial ischemia. The majority (53.8%) of treated lesions were located left anterior descending artery, with each group showing a similar tendency. Bare metal stents were employed in 53.8%, drug eluting stents in 36.5%, and no stent was applied 9.6%; these trends were also similar in each group.

Medication and treatment

Before catheterization, patients had only received drugs for each disorder regarding coronary risk factor, and less than 30% of patients received anti-platelet therapy. One patient who did not receive aspirin had a history of aspirin-induced drug eruption, and only received ticlopidine. Eight patients underwent ticlopidine discontinuation, because of drug eruption or liver damage induced by it, 7 patients changed to cilostazol, and one patient was administered a double-dose of aspirin. Patients exhibited a high rate of receiving multiple, evidenced-based therapies [1] (Table 2).

Clinical outcomes

In this study population, there was no periprocedural complication such as death, myocardial infarction, acute or subuacte stent thrombus, or repeat PCI. Overall, the follow-up period 255 ± 115 days, with no significant difference among 3 groups. There were no out-of-hospital cardiac events such as target lesion revascularization. Further, no patients experienced gastro-intestinal hemorrhage.

LV volume and pressure

Table 3 shows data on LV volume and pressure. LV volume and pressure revealed no significant difference between baseline and follow-up data among the 3 groups. We also investigated rate of changes in LV volume and pressure in each group (Fig. 2). The rate of changes in EF in group P showed significantly greater decrease than in the control group (C: $3.8 \pm 9.8\%$, P: $-2.1 \pm 5.9\%$, $p < 0.05$), and that in group H showed a decreasing tendency (H: $-1.6 \pm 7.6\%$, ns compared to control). The change rate of ESVI in group P showed was significantly greater increase than that in the control group (C: $-4.5 \pm 16.2\%$, P: $7.3 \pm 16.2\%$, $p < 0.05$), and that in group H showed an increasing tendency (H: $4.9 \pm 15.5\%$, ns compared to control). The rate of changes in EDVI were similar among three groups (C: $2.5 \pm 8.9\%$, H: $2.6 \pm 3.6\%$, and P: $1.6 \pm 6.1\%$, ns). The rate changes in $+dp/dt$ and magnitudious $-dp/dt$ revealed no significant differences among the 3 groups. However, these parameters showed a decreasing tendency in H group ($+dp/dt$: C: $3.9 \pm 15.5\%$, H: $-10.0 \pm 25.2\%$, and P: $0.3 \pm 19.6\%$, magnitudious $-dp/dt$: C: $-0.1 \pm 19.5\%$, H: $-8.5 \pm 20.4\%$, and P: $5.7 \pm 27.7\%$).

Other factors related to changes in LV volume and pressure

Table 4 shows the relationships between LV volume, pressure, and other variables: patients characteristics, angiographic and intervention backgrounds, and adjunct drugs. Multi-vessel PCI was significantly correlated with EF and ESVI. RCA and $+dp/dt$ were also significantly correlated. Regarding adjunct drugs, only aspirin was associated with $+dp/dt$. However, these variables showed similar overall tendency in this study.

Discussion

The present findings indicated that: (1) chronic administration of PPI could significantly decrease the rate of changes in EF, increase that in ESVI compared with the control; (2) high-dose H2-blocker administration tended to decrease the rate of changes in EF, increase that in ESVI compared with the control, and also tended to decrease that in the magnitude of positive dp/dt and magnitudious of negative dp/dt; (3) other drugs except for aspirin do not effect the change in cardiac function.

Patients with ischemic heart disease require intensive treatment including therapies involving aspirin and anti-platelet [1,2]. Especially, ischemic heart disease patients receiving PCI with coronary stent must continue taking aspirin, ticlopidine or clopidogrel [1,2,9,10]. NSAIDs-related ulcer should

Table 1 Patients' characteristics, angiographic and intervention backgrounds

	Total	(%)	Control	(%)	*p*	(%)	H	(%)	*p*-Value
n	52		16		28		8		
Patients' characteristic									
Age (y.o.)	65.1 ± 9.5		62.5 ± 7.4		662 ± 11.8		66.3 ± 5.3		
Male	33	63.5	11	68.8	17	60.7	5	62.5	ns
Diabetes mellitus	19	36.5	9	56.3	3	10.7	7	87.5	ns
Hypertension	38	73.1	13	81.3	17	60.7	8	100.0	ns
Hyperlipidemia	28	53.5	9	56.3	17	60.7	2	25.0	ns
Smoker	14	26.9	1	63	11	39.3	2	25.0	$p < 0.05$
Angiographic and intervention background									
Single vessel disease	27	51.9	5	31.3	18	64.3	4	50.0	ns
Two vessel disease	12	23.1	5	31.3	5	17.9	2	25.0	ns
Three vessel disease	13	25.0	6	37.5	5	17.9	2	25.0	ns
Multi-vessel intervention	7	13.5	3	18.8	3	10.7	1	12.5	ns
Target vessel									
Left anterior descending	28	53.8	8	50.0	15	53.6	5	62.5	ns
Left circumflex	16	30.8	6	37.5	8	28.6	2	25.0	ns
Right	18	34.6	6	37.5	10	35.7	2	25.0	ns
Intervention device									
Drug eluting stent	19	36.5	5	31.3	10	35.7	4	50.0	ns
Bare metal stent	28	53.8	11	65.8	15	53.6	2	25.0	ns
POBA or CB alone	5	9.6	0	0.0	3	10.7	2	25.0	ns
Follow-up period (days)	255 ± 115		288 ± 158		238 ± 100		252 ± 53		ns

Ages and follow-up days are expressed as the mean ± S.D. POBA: plain old balloon angioplasty; CB: cutting balloon angioplasty. There was a significant difference in the number of smokers between the control and group P ($p < 0.05$).

Table 2 Prescribed drugs

	Previous prescribed drug				Adjunct drugs				Prescribed drugs at follow-up			
	Total	Control	P	H	Total	Control	P	H	Total	Control	P	H
n	52	16	28	8	52	16	28	8	52	16	28	8
Asprin	11	5	4	2	40	10	24	6	51	15	28	8
Ticlopidine	2	1	1	0	41	13	24	4	43	14	25	4
Cilostazol	2	1	1	0	5	1	1	3	7	2	2	3
β-Blocker	5	3	2	0	3	0	2	1	8	3	4	1
α-Blocker	2	1	1	0	1	0	1	0	3	1	2	0
Ca-blocker	25	11	10	4	6	0	6	0	31	11	16	4
ARB/ACE	23	7	10	6	6	1	4	1	29	8	14	7
Statin	13	6	5	2	9	1	8	0	22	7	13	2
Fibrate	1	0	0	1	2	1	1	0	3	1	1	1
Nicorandil	8	5	2	1	15	3	11	1	23	8	13	2
Nitrate	7	2	4	1	11	3	6	2	18	5	10	3
Diuretics	5	4	1	0	3	2	1	0	8	6	2	0
Insulin	8	4	2	1	0	0	0	0	7	4	2	1
α-GI	8	4	2	2	0	0	0	0	8	4	2	2
Sulforrlurea	7	1	4	2	0	0	0	0	7	1	4	2
Metformin	6	3	3	0	0	0	0	0	6	3	3	0
Pioglitazone	1	1	0	0	0	0	0	0	1	1	0	0

ARB: angiotensin II receptor blocker; ACE: angiotensin converting enzyme inhibitor; α-GI: α-glucosidase inhibitor.

be prevented because its development may lead to the necessity to discontinue anti-platelet therapy. PPI and high-dose H2-blocker, even though their adverse cardiac effects were reported previously [4,7], are currently applied to prevent NSAIDs-related ulcer. Generally, many cardiologists are unaware of the negative aspects of PPI and high-dose H2-blocker. Although *in vitro* study of H2-blocker and PPI [4,7] and an a short-term, human, *in vivo* study documented negative cardiovascular effect [6,7], the cardiac effects of PPI and H2-blocker on long-term administration have scarcely reported.

H^+/K^+-ATPase could contribute significantly to the regulation of myocardial K^+ and H^+ homeostasis. The inhibition of H^+/K^+-ATPase might therefore induce cellular acidosis, which is known to inhibit myocardial contractility mainly at the level of the myofilament. Schillinger et al. assessed this negative inotropic effect using pantoplazole *in vitro*

Table 3 LV volume and pressure assessed by left ventricular angiography

	Total	Control	H	P
EF (%)				
Baseline	70.5 ± 8.0	67.9 ± 10.6	68.9 ± 7.7	72.4 ± 5.8
Follow-up	70.0 ± 7.0	69.7 ± 9.1	67.8 ± 8.7	70.7 ± 5.1
EDVI (ml/m^2)				
Baseline	79.2 ± 13.5	77.5 ± 14.7	77.1 ± 13.5	80.7 ± 13.1
Follow-up	80.7 ± 13.2	79.9 ± 16.6	79.0 ± 13.4	81.6 ± 11.6
ESVI (ml/m^2)				
Baseline	23.5 ± 7.7	25.3 ± 10.6	23.6 ± 5.7	22.4 ± 6.1
Follow-up	23.9 ± 7.1	23.9 ± 9.3	24.8 ± 7.6	23.6 ± 5.8
+d*p*/d*t* (mmHg/s)				
Baseline	2252 ± 592	2184 ± 645	2194 ± 80	2305 ± 623
Follow-up	2213 ± 554	2258 ± 505	1944 ± 439	2264 ± 587
Magnitudious −d*p*/d*t* (mmHg/s)				
Baseline	2440 ± 555	2433 ± 607	2470 ± 403	2436 ± 580
Follow-up	2413 ± 550	2404 ± 669	2221 ± 439	2478 ± 512

Data are the mean ± S.D. There were no significant differences among the 3 groups, as well as between the baseline and follow-up.

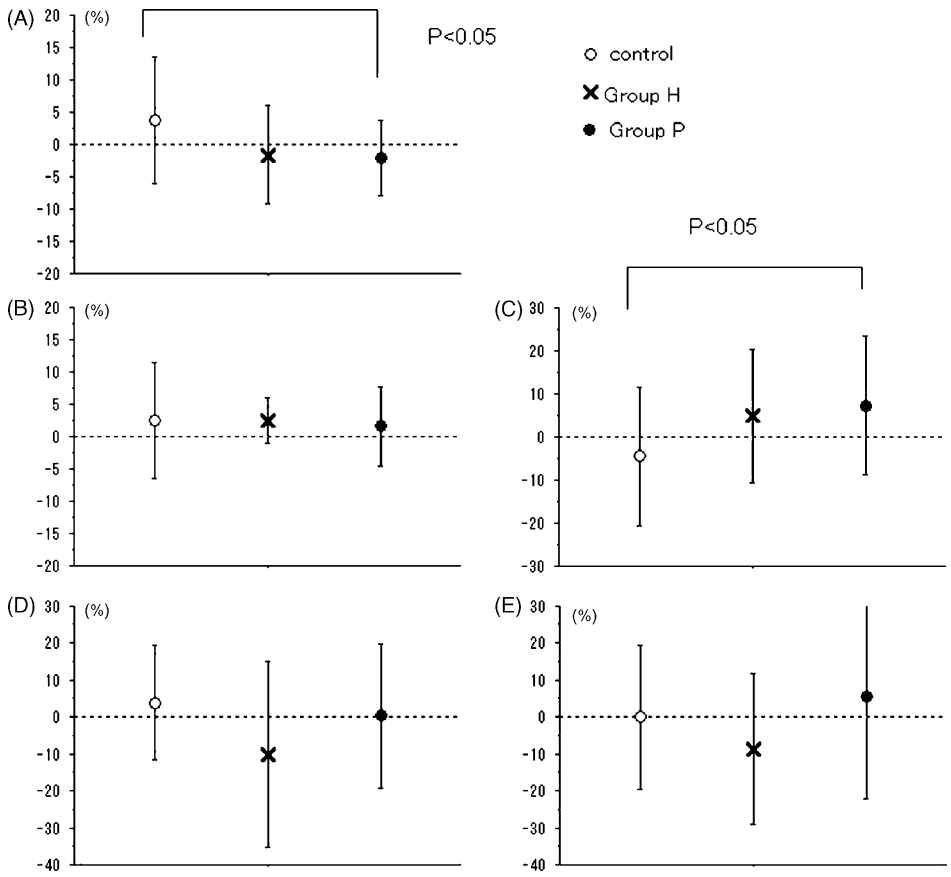

Figure 2 Comparison of rate of changes in LV volume and pressure among the 3 groups. Bars represent the mean ± S.D. of each parameter with changes between baseline and follow-up. (A) The rate of change in EF. The values were: 3.8 ± 9.8% for the control, −1.6 ± 7.6% for group H, and −2.1 ± 5.9% for group P. There were significant differences between the control and group P. (B) The rate of change in EDVI. The values were: 2.5 ± 8.9% for the control, 2.6 ± 3.6% for group H, and 1.6 ± 6.1% for group. There were no differences among the 3 groups. (C) The rate of change in ESVI. The values were: −4.5 ± 16.2% for the control, 4.9 ± 15.5% for group H, and 7.3 ± 16.2% for group P. There were significant difference between the control and group P. (D) The rate of change in +d*p*/d*t*. The values were 3.9 ± 15.5% for the control, −10.0 ± 25.2% for group H, and 0.3 ± 19.6% for group P. There were no significant differences among the 3 groups. (E) The rate of change in maginitudious −d*p*/d*t*. The values were −0.1 ± 19.5% for the control, −8.5 ± 20.4% for group H, and 5.7 ± 27.7% for group P.

[7]. In that work, a concentration of 6.25 μg/ml induced a reduction of the contractile force of isolated trabeculae by 27 ± 9%, which is similar to the clinical concentration of 4.6 μg/ml due to 40 mg pantoprazole [11] commonly orally administration. Katashima et al. reported that pantoplazole exhibited a slightly weaker inhibition of acid secretion than lansoplazole [12]. They also showed that the relation between the plasma concentration and inhibitory effect on PPIs could be assessed by pharmacokinetic/pharmacodynamic analysis, and the chronic administration of PPI could stabilized the acid inhibitory rate to some extent. Though the concentration of pantoplazole (15 mg) was half of that previously applied (30 mg) [13], a previously report showed that 15 mg lansoprazole could inhibit NSAIDs-related ulcer development as effectively as 30 mg [14]. It may be that lansoplazole was a stronger H^+/K^+-ATPase inhibitor than pantoplazole, leading to a negative effect on cardiac function. However, the mean rate of change in EF was −2.1%, and that of ESVI was 7.3%. These were smaller decreases than predicted by an *in vitro* study, suggesting that the chronic administration of lansoplazole affects cardiac function only slightly. One reason is that PPI also exhibits a positive inotropic effect in atria. Yenisehirli and Onur observed this effect of PPI in rat atria, and that it was potentiated by pretreatment with the Na^+/K^+-ATPase inhibitor ouabain. Moreover, lansoprazole induced a prolongation of the action potential. The authors speculated that this could be mediated by the inhibition of H^+/K^+-ATPase, promoting altered intracellular Ca^{2+} movement [15].

Table 4 Variables of repeated-measures ANOVA

	EF	EDVI	ESVI	+d*p*/d*t*	−d*p*/d*t*
Patients' characteristics					
Age (y.o.)	0.49	0.31	0.71	0.02	0.81
Male	0.29	0.53	0.13	0.78	0.46
Diabetes mellitus	0.57	0.40	0.43	0.79	0.6
Hypertension	0.94	<0.05	0.89	0.49	0.37
Hyperlipidemia	0.75	0.23	0.71	0.6	0.43
Smoker	0.39	0.79	0.21	0.68	0.98
Angiographic and intervention background					
Single vessel disease	0.28	0.48	0.41	0.67	0.22
Two vessel disease	0.62	0.61	0.74	0.31	0.52
Three vessel disease	0.43	0.74	0.52	0.92	0.74
Multi-vessel intervention	<0.01	0.42	<0.01	0.83	0.54
Target vessel					
Left anterior descending	0.59	0.73	0.75	0.2	0.12
Left circumflex	0.19	0.52	0.47	0.28	0.5
Right	0.24	0.89	0.12	<0.05	0.07
Intervention device					
Drug eluting stent	0.42	0.99	0.55	0.65	0.34
Bare metal stent	0.16	0.72	0.20	0.4	0.94
POBA or CB alone	0.38	0.55	0.28	0.27	0.3
Adjunct drug					
PPI/H2-blocker	0.07	0.82	0.08	0.36	0.43
Asprin	0.53	0.94	0.55	<0.05	0.82
Ticlopidine	0.86	0.44	0.63	0.7	0.92
Cilostazol	0.75	0.58	0.94	0.14	0.19
β-Blocker	0.07	0.74	0.07	0.25	0.68
α-Blocker	0.49	0.14	0.52	0.09	0.54
Ca-blocker	0.94	0.86	0.92	0.83	0.37
ARB/ACE	0.68	0.93	0.07	0.84	0.56
Statin	0.74	0.09	0.64	0.56	0.75
Fibrate	0.78	0.26	0.57	0.59	0.88
Nicorandil	0.18	0.54	0.34	0.66	0.07
Nitrate	<0.05	0.11	0.18	0.59	0.84
Diuretics	0.86	0.82	0.99	0.91	0.58

POBA: plain old balloon angioplasty; CB: cutting balloon angioplasty; ARB: angiotensin II receptor blocker; ACE: angiotensin converting enzyme inhibitor.

On the other hand, histamine exerts inotropic effects via H2-receptors, such as enhancing ventricular contraction and increasing the sinus rate. Several adverse effects such as bradycardia, sinus arrest, atrio-ventricular conduction disturbances, and cardiac decompensation have been linked to the use of H2-blockers [4]. However, these mostly show spontaneous recovery. These effects occurred on intravenous administration at a very high-dose (more than 100 mg on in a single bolus). In general, changes in cardiac performance are modulated by the autonomic nervous system, and physiological homeostasis is preserved. Therefore, changes in autonomic nervous activity and/or sympathovagal balance may be involved in the cardiovascular effects. Further, cardiovascular effects of H2-blocker may be related to the autonomic nervous system, and modulated activity, and/or sympathovagal balance [5].

In previous reports, PPI and H2-blocker decreased cardiac function, but controversy existed. Although our study compared pre and follow-up PCI, the cardiac function showed no marked changes on long-term administration. In ischemic heart disease patient, other medicines such as β-blocker, Ca-blocker, or diuretics have a strong effect, and PPI and H2-blocker would have a weak influence on cardiac function.

Aspirin and other anti-platelet drugs are essential for patients with ischemic heart disease [1,2], and when physicians or patients are anxious regarding the weak adverse effects of PPI or H2-blocker

on cardiac function, and cease to take these drugs, the risk of NSAIDs-related peptic ulcer is high [3]. In the presence of an active ulcer, anti-platelet drugs must be discontinued in some patients. In this case, the risks of cardiac event such as stent thrombus are increased [2], particularly in patients undergoing drug eluting stent implantation [9,10]. Additionally, patients with ischemic heart disease exhibit multiple disorders such as hypertension, diabetes mellitus and chronic kidney disease. A low hemoglobin level together with chronic kidney disease increases the risk of coronary heart disease-related death [16]. Attempts should be made in patients with ischemic heart disease and chronic kidney disease to reduce the risk of anemia, such as protecting against gastro-intestinal hemorrhage. To prevent NSAIDs-related, ulcer should be used PPI or H2-blocker should be administered.

In conclusion, the long-term administration of PPI and high-dose H2-blocker does not marked alter cardiac function. Cardiologists should not hesitate to use them, due to concerns over any cardiac function inhibitory effect.

Study limitations

This study had several important limitations. It was a retrospective, non-randomized study in which the study population was small and the results reflect the experience of only a single center. It, therefore, lacks the obvious advantages of a larger, multicenter, multinational randomized study. Inclusion criteria of this study were too restrictive to limit number of the study patients. This led that the present study might be underpowered for the detection of the changes by PPI or H2-blocker. However, most patients with coronary heart disease who had a prior cardiac catheterization study had already administrated PPI or H2-blocker. Additionally cardiac function of patients prior revascularization with unstable angina, myocardial infarction, congestive heart failure could be greatly affected by revascularization or other drugs such as β- and Ca-blocker, diuretics, and ARB/ACE. To investigate effects of PPI or H2-blocker, these cases might have bias in a single-center experience. It is important issue which could affect the clinical practice for patients with coronary heart disease receiving PPI or H2-blocker for prevention of such aspirin- or NSAIDs-related peptic ulcers. Therefore, it should be investigated in a further study of larger, multicenter, multinational randomized study including patients with LV dysfunction.

We recorded LV pressure with a pig-tail catheter, and dp/dt values lacked the accuracy of those measured using a micro-manometer-tipped catheter.

Conflict of interest

All authors had no conflict of interest.

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